REMARKS

Claims 1-4, 7, 9-12, 14-33, 35-42, 45-53 and 55 are rejected. Claim 1 has been amended. Claims 16 and 17 have been canceled. New claims 56 and 57 have been added. Claims 1-4, 7, 9-12, 14-33, 35-42, 45-53, 55, 56 and 57 are presently pending in the application. Favorable reconsideration of the application in view of the following remarks is respectfully requested.

The basis for the amendment of claim 1 is found in claim 17 as originally filed, pg. 7, lines 10-11 (water-insoluble), and pg. 6, line 29, pg. 9, lines 26-30, and pg. 8 line 27 (water-soluble) of the specification as originally filed. The basis for new claim 56 is found in claims 1, 17 and 25 as originally filed. The basis for the addition of new claim 57 is previously canceled claim 44, re-introduced herein as originally filed.

Rejection Under 35 U.S.C. §103(a):

The Examiner has rejected Claims 1-4, 7, 9-12, 14-24, 27-30, 32, 33, 35-42, 45-53, and 55 under 35 U.S.C. 103(a) as being unpatentable over Glazer et al. (WO 00/61282, Oct. 19, 2000) in view of Sutton et al. (U.S. Patent No. 5,714,340, Feb. 3, 1998), Yao et al. (U.S. PG Pub. No. US 2003/0100086 Al, filed May 30, 2001), and Obana (U.S. Patent No. 4,605,686, Aug. 12, 1986), and in light of Pierce et al. (U.S. Patent No. 4,258,001, Mar. 24, 1981), indicating that Glazer et al. teaches a microarray comprising a porous silica substrate, which offer an increase in array density and signal enhancement over conventional flat glass substrates, the porous substrate provides a large surface area for biological polymers such as nucleic acids, polynucleotides, polypeptides, and polysaccharides to be attached to make an array, a porous layer is formed on a substrate material and in some embodiments, the porosity, pore size, and thickness of the porous layer is chosen according to desired functionalization characteristics, porous substrates are generated by creating a 3D matrix to increase the surface area and therefore increase the number of sites available for array synthesis in the same lateral dimensions, one advantage of using a porous layer is to increase the effective surface are to make an array that can be functionalized with a much higher density of polymers for a given two dimensional or "flat" area without changing the spacing between cells of the array on the substrate surface, the effective surface area is the surface area of the porous region that is available for adsorption of polymer molecules or for polymer

synthesis, and Glazer et al. further teaches a bioaffinity tag bound to the porous layer localized in a spatially addressable manner and Sutton et al. teaches that antibodies are bound to the polymer particle of the porous layer. The Examiner notes that Glazer et al. fails to teach a porous layer comprising monodisperse polymer particles having a mean diameter between 0.05 to 50 microns and a particle size distribution with a coefficient of variation less than 20% and fails to teach a microarray, wherein the chemically active groups such as carboxylic acids, primary amines and secondary amines are present on stabilizer polymers, which are covalently grafted, chemisorbed, or physically absorbed to the surface of the polymer particles, but Sutton et al. teaches a porous layer comprising polymer particles having a diameter in the range of 0.1 to 5 microns and a hydrophilic polymer, the porous layer provides a substrate for immobilizing receptor such as antibodies while avoiding inactivation, which results in low sensitivity, active groups such as vinylsulfonyl group can be directly attached to polymer particles for covalent attachment of receptor to the particles, and that polymer particles can be composed of a wide variety of organic polymers, including both natural and synthetic, and preferably are composed of one or more addition polymers described in Pierce et al, which teaches a particulate structure on a support surface containing interactive compositions (bioaffinity tags) useful for the analysis of various substances in liquids. The Examiner continues that Pierce teaches the interactive compositions if present in the particulate structure can be immobilized therein to minimize or prevent undesired migration of the composition within the structure or other zones of an element containing the particulate structure, immobilization can be effected by a variety of means including physical absorption and chemical bonding to the particles of the structure, for example, particles, which are prepared from polymers containing an active linking or bonding site can advantageously be chemically bonded to one or more components of a particular interactive composition by establishing a covalent bond between this site and a reactive group of the interactive component, addition polymers having reactive groups such as vinyl benzylamine, which contains primary, secondary or tertiary amino group, the particulate structure can readily take up, uniformly distribute within itself, meter, rapidly transport applied liquid samples containing any of a wide variety of analytes and is particularly suited for immunoassay, making it obvious to one of ordinary skill in the art at the

time of the invention to realize that polymer particles of Sutton et al. would comprise addition polymers (stabilizer polymer) of Pierce et al. physically absorbed to the surface of the polymer particles for immobilization of interactive compositions such as antibodies via active linking or binding site such as primary and secondary amine groups. The Examiner also indicates Yao et al. teaches that porous polymeric material having polymeric particles having a narrow size distribution can be consistently packed into molds, and a narrow particle size distribution allows the production of substrate with a uniform porosity, as solutions and gases tend to flow more evenly through uniformly porous materials than those, which contain regions of high and low permeability, uniformly porous substrates are also less likely to have structural weak spots than substrates, which comprise unevenly distributed pores of substantially different sizes, while Obana et al. teaches a method of producing polymer (latex) particles with uniform diameters having coefficient of variation in the range of 5% or less within each batch, making it obvious to one of ordinary skill in the art at the time of the invention to substitute the porous layer in the microarray of Glazer et al. with a porous layer comprising polymer particles having small diameter in the range of 0.1 to 5 microns as taught by Sutton et al. to provide a substrate for immobilizing receptors such as antibodies with an advantage of having enhanced sensitivity and providing larger effective surface area for available for adsorption of biological polymers such as antibodies, as the larger effective surface area provided by smaller diameter of polymeric particles as taught by Sutton et al. would provide an array that can be functionalized with a much higher density of biological polymers for a given two dimensional or "flat" area without changing the spacing between cells of the array on the substrate surface thereby increasing sensitivity of the microarray, and, in addition, making it obvious to one of ordinary skill in the art at the time of the invention to use polymeric particles having a narrow size distribution with coefficient of variation of polymer particle diameter in the range of 5% of less as taught by Obana since porous polymeric material having polymeric particles having a narrow size distribution (i.e. particles of about the same size) can be consistently packed into molds, and a narrow particle size distribution allows the production of substrate with a uniform porosity as taught by Yao et al, as having a substrate with uniform porosity is advantageous because solutions and gases tend to flow more evenly through uniformly porous materials

than those, which contain regions of high and low permeability, and uniformly porous substrates are also less likely to have structural weak spots than substrates, which comprise unevenly distributed pores of substantially different sizes.

Glazer relates to methods for making and using thin films of porous silica substrates to synthesize arrays of polymers and methods for assaying such polymers on porous silica substrates. The porous silica substrates offer an increase in array density and signal enhancement over conventional flat glass substrates. Examples of polymers that can be synthesized and assayed include biological polymers such as nucleic acids, polynucleotides, polypeptides, and polysaccharides. Arrays of nucleic acids or polynucleotides can be used for a variety of hybridization-based experiments such as nucleic acid sequence analysis, nucleic acid expression monitoring, nucleic acid mutation detection, speciation, effects of drug therapy on nucleic acid expression, among others.

Sutton relates to a dry immunoassay analytical element, for assaying a ligand comprising, in the following order, (a) a layer containing a labeled ligand, (b) a bead spreading layer, c) a cross-linked hydrophilic polymer layer and d) a support; wherein a fixed concentration of an immobilized receptor for the labeled ligand is located in a zone at the interface of layers (b) and (c); and the receptors are immobilized by being covalently bonded to polymeric beads that are smaller than the beads in layer (c).

Pierce discloses an element for the analysis or transport of liquid, especially aqueous liquids, containing a structure comprising a plurality of heat-stable, organo-polymeric particles non-swellable in and impermeable to the liquid, and an adhesive concentrated at particle surface areas contiguous to adjacent particles bonding the particles into a coherent, three-dimensional lattice that is non-swellable in the liquid. These structures are particularly useful in the "dry chemistry" analysis of aqueous liquids. "Dry chemistry" analysis refers to analytical methods and techniques that are carried out using chemical reagents contained in various "dry-to-the-touch" test elements such as "dip-and-read" test strips, multilayer test elements and the like.

Yao relates to porous polymeric materials comprising a porous polyolefin substrate containing inclusions of a material to which chemical or biological moieties are attached directly or via a spacer, methods of making them, and applications in medical devices.

Obana relates to a latex for immunoserological tests containing polystyrene and/or polystyrene derivative particles which are prepared by polymerizing styrene and/or styrene derivatives in the absence of emulsifying agents, said particles having uniform diameters and a specific gravity of 1.05 or more.

The present invention relates to a microarray comprising a support having attached to a surface thereof at least one porous layer, wherein said porous layer comprises a hydrophilic binder and water-insoluble polymer particles comprising a particle size distribution with a coefficient of variation of less than 20% and having a mean diameter of from 0.05 to 50 microns. The water-insoluble polymer particles comprise chemically active groups on water-soluble stabilizer polymers which are covalently grafted, chemisorbed, or physically adsorbed to the surface of the water-insoluble polymer particles, and which comprise pendant vinylsulfonyl or latent vinylsulfonyl groups and are represented by Formula I, and further comprising a bioaffinity tag bound to the porous layer in a spatially addressable manner.

To establish a prima facia case of obviousness requires, first, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combines) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

The reference to Sutton fails to teach the modification required by the present invention, that is, the monodispersed particles of the present invention and monodispersed water soluble polymer beads stabilized by vinylsulfonyl-functionalized polymers, which are grafted to the surface of the bead, which are stable and dispersible in aqueous systems. Pierce discloses a plurality of heat-stable, organo-polymeric particles non-swellable in and impermeable to the liquid for use in "dry chemistry" applications, not water insoluble polymer particles that are stabilized by water soluble vinylsulfonyl-functionalized polymers. Pierce also fails to teach a porous layer containing a hydrophilic polymer in combination with

a polymer bead, or a hydrophilic polymer in combination with a water-insoluble polymer bead bearing stabilizing, water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead. Glazer teaches a porous layer of, typically, silica particles, but fails to disclose a porous layer containing a hydrophilic polymer in combination with a polymer bead, or a hydrophilic polymer in combination with a water-insoluble polymer bead bearing stabilizing, water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead. Yao discloses appropriately sized particles, but fails to mention the use of hydrophilic binders for use with insoluble beads in the porous layer, teaching instead hydrophobic binders at [0058]. Yao also fails to teach water insoluble particles which are stabilized in water-based systems by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead and fails to teach the presence of bioaffinity tags in the porous layer, placing the tags instead exterior to the layer. See, for example Fig. 1. Obana teaches a polymer particle with a particular size variation, but fails to teach a porous layer of hydrophilic binder and water insoluble beads, water insoluble beads which are stabilized in water-based systems by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead, and fails to mention microarrays. Therefore, the references, alone and in combination, fail to teach, suggest or provide a disclosure to modify the references to produce water insoluble polymer beads stabilized by water soluble vinylsulfonyl-functionalized polymers, which are grafted to the surface of the bead.

In fact, the references to Sutton, Pierce and Glazer are not combinable. MPEP 2143.01 Section V states "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)." MPEP 2143.01 Section VI indicates "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under

which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.)." Glazer and Pierce fail to disclose the use of a binder in the porous layer with the particles. Sutton utilizes a binder matrix with the polymer bead. Sutton indicates, at col. 7, lines 28-32, that coating without polymers results in an inoperative element. Sutton specifically mentions that coatings as disclosed in Pierce were inoperative. Accordingly, a combination of glazer and Pierce with Sutton would render the element inoperable or at least so change the principals of operation as to require substantial reconstruction and redesign.

The references also fail to provide any likelihood of success, as there is no teaching to suggest the preparation of particles useful in aqueous systems. None of the references provide a likelihood that the modification of a water insoluble bead with water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead will produce polymer bead, which is stable in aqueous systems and combinable with hydrophilic binders. Pierce teaches the use of the particles in " dry chemistry" systems (col. 1, lines 8-15). Sutton specifically indicates the particles are water-insoluble (Abstract). Glazer, as noted by the Examiner, fails to teach stabilizer polymers attached to the surface of the bead. Yao and Obana fail to mention combining a hydrophilic binder with a water insoluble polymer particle in a porous layer. The references, alone and in combination, fail to provide any likelihood of success in producing a particle, made compatible with hydrophilic binders by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead for use in a porous layer. The Examiner notes benefits such as "*low sensitivity, active groups such as vinylsulfonyl group can be directly attached to polymer particles for covalent attachment of receptor to the particles*," and "*Pierce et al. physically absorbed to the surface of the polymer particles for immobilization of interactive compositions such as antibodies via active linking or binding site such as primary and secondary amine groups.*" These benefits differ from the present invention, in which the purpose of the graft, functionalized polymer is to impart water compatibility to a water insoluble particle, making the particle not only useful in hydrophilic systems, but also resulting in simpler, milder manufacturing conditions. See the present specification, pg. 9, lines 25-30 ("*G is a polymerized α,β-ethylenically unsaturated addition polymerizeable monomer which imparts*

desirable solubility properties to the polymer or which allows the polymer particles of this invention to be readily dispersed in a carrier solvent (water in most cases)"); pg. 9, lines 7-12 ("*In an especially preferred embodiment, the polymer particles contain stabilizer polymer comprising pendant vinylsulfonyl or latent vinylsulfonyl groups. Stabilizer polymers having activated vinylsulfonyl groups possess additional advantages in that proteins may be attached to the polymers under milder conditions and utilize less process control during manufacture. This renders manufacture more efficient and less costly.*"); pg. 8, lines 14-19 ("*In a preferred embodiment, the polymer particles are rich in specific functionalities, which impart dispersibility in a desired carrier solvent, compatibility with the microarray's matrix*")

The references also fail to include all of the present claim limitations, since the references fail to disclose porous layer of hydrophilic binder and water insoluble beads, water insoluble beads that are stabilized in water-based systems by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead.

The combination of the references would produce a water-insoluble particle, which would be incompatible in a hydrophilic binder. The present particle, as a result of the grafted vinylsulfonyl-functionalized polymers, which are soluble in water, water-miscible solvents, or a mixture thereof, are stabilized in hydrophilic combination. In addition, the present invention would have increased activity, as indicated in the present specification on pg. 3, lines 3-17, as the present invention combines a scaffold concept with a porous layer. Although, as noted by the Examiner, a porous substrate increases surface area, a porous layer with particles bearing a three-dimensional region of polymer would further increase the surface area available for binding, beyond that available with a porous layer alone.

In summary, the references fail to disclose, teach or suggest the present invention wherein a vinylsulfonyl-functionalized polymer, which is soluble in water, is grafted to the surface of the monodisperse, water insoluble, polymer bead, fail to provide any likelihood of success for the use of monodispersed beads which are stabilized by a vinylsulfonyl-functionalized polymer, which is soluble in water, water-miscible solvents, or a mixture thereof, is grafted to the surface of the monodispersed, water insoluble, polymer bead,

resulting in the stability and dispersibility of these grafted polymer particle in aqueous systems, and fails to include the limitation that the polymer beads include a vinylsulfonyl-functionalized polymer, which is soluble in water, water-miscible solvents, or a mixture thereof, grafted to the surface of the monodisperse, water insoluble, polymer bead. The Applicants therefore request that the Examiner reconsider and withdraw the rejection.

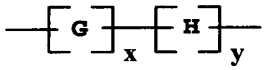
Claims 2-4, 7, 9-12, 14-24, 27-30, 32, 33, 35-42, 45-53, and 55 benefit from dependence on claim 1 which as discussed above, Applicants believe is non-obvious with respect to the references.

Rejection of Claims 25 and 26 Under 35 U.S.C. §103(a):

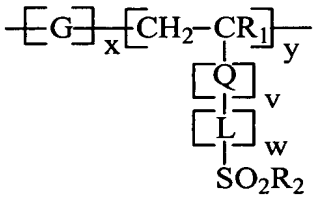
The Examiner has rejected Claims 25 and 26 under 35 U.S.C. 103(a) as being unpatentable over Glazer et al. (WO 00/61282, Oct. 19, 2000) in view of Sutton et al. (U.S. Patent No. 5,714,340, Feb. 3, 1998), Yao et al. (U.S. PG Pub. No. US 2003/0100086 Al, filed May 30, 2001), and Obana (U.S. Patent No. 4,605,686, Aug. 12, 1986), and in light of Pierce et al. (U.S. Patent No. 4,258,001, Mar. 24, 1981) as applied to claims 1, 16, and 17 above, and further in view of Ogawa et al. (U.S. Patent No. 4,548,869, Oct. 22, 1985), indicating that Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. teaches a microarray comprising a stabilizer polymer as discussed above, Pierce et al. teaches a particulate structure on a support surface containing interactive compositions (bioaffinity tags) useful for the analysis of various substances in liquids, the interactive compositions if present in the particulate structure can be immobilized therein to minimize or prevent undesired migration of the composition within the structure or other zones of an element containing the particulate structure, immobilization can be effected by a variety of means including physical absorption and chemical bonding to the particles of the structure, the particles, which are prepared from polymers containing an active linking or bonding site can advantageously be chemically bonded to one or more components of a particular interactive composition by establishing a covalent bond between this site and a reactive group of the interactive component, Pierce et al. teaches addition polymers (stabilizer polymer) comprising a monomer blend containing from monomers selected from groups (a)-(k) such as acrylamide having a cross-linking vinylsulfonyl group , the particulate structure can readily take up, uniformly distribute within itself, meter, rapidly transport applied liquid

samples containing any of a wide variety of analytes, and is particularly suited for immunoassay, Sutton et al. teaches a coating layer comprising polyacrylamide, which does not adversely affect the activity of antibody receptors immobilized on the polymer particles, and a further advantage is achieved by forming uniform coating as the viscosity of the polymers increases substantially resulting in a "set layer" that remains stable and uniform during wet transport and drying of the polymers. The Examiner notes that, although Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. fails to teach a microarray, wherein the vinylsulfone or vinylsulfone precursor "H" of Formula I represents groups represented by Formula II:

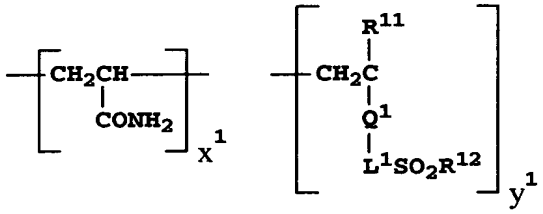
Formula I



Formula II



, Ogawa et al. teaches an adhesive layer to improve adhesion between a plastic support and a polyacrylamide gel medium and the adhesive layer comprising a polymer having at least one specifically selected repeated unit having the following formula:



in which R^{11} is a hydrogen atom or an alkyl group containing 1-6 carbon atoms; Q^1 is -COO-, $CON(R^{11})$- or an arylene group containing 6-10 carbon atoms; L^1 is a divalent group containing at least one linkage selected from the group consisting of -COO- and $-CON(R^{11})$- and containing 3-15 carbon atoms, or

divalent atom containing at least one linkage selected from the group consisting of -0-, -N(R^{11})-, -CO-, -SO-, -SO2-, -S03-, -S02N(R^{11}) -, -N(R^{11})CON(R^{11}) and -N(R^{11})C00-, and containing 1-12 carbon atoms, in which R^{11} has the same meaning as defined above; R^{12} is -CH=CH_2 or-$CH_2CH_2X^1$, in which X^1 is a substituent replaceable with a nucleophilic group or releasable in the form of HX^1 by a base and x^1 and y^1 both representing molar percentage range from 0 to 99 and from 1 to 100, respectively, and x^1+y^1 is not less than 90 (column 2, line 47-column 3, line 12), Ogawa et al. further teaches a process for synthesis of ethylenic unsaturated monomers containing a vinylsulfonyl group or function group convertible into vinylsulfonyl group, which are employable for the preparation of polymers comprising repeating unit represented by the formula above, making it obvious to one of ordinary skill in the art at the time of the invention to use adhesive layer having the formula of Ogawa et al. as a stabilizer polymer composition comprising vinylsulfone or vinylsulfone precursor "H" of in the polymer particle of Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. as the adhesive layer of Ogawa et al. provides functional groups such as vinylsulfonyl group for immobilization of interactive compositions such as antibodies while improving adhesion between the plastic support (polymer particles) and coating layer comprising polyacrylamide of Sutton et al, since the advantage of improving adhesion between the polymeric particles and coating layer provides the motivation to combine the teachings of Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. and Ogawa et al. with a reasonable expectation of success as the polyacrylamide coating layer of Sutton et al. would adhere to the polymeric particle comprising stabilizer polymer composition comprising vinylsulfone or vinylsulfone precursor "H" of in the polymer particle.

The present invention relates to a microarray comprising a support having attached to a surface thereof at least one porous layer, wherein said porous layer comprises a hydrophilic binder and water-insoluble polymer particles comprising a particle size distribution with a coefficient of variation of less than 20% and having a mean diameter of from 0.05 to 50 microns. The water-insoluble polymer particles comprise chemically active groups on water-soluble stabilizer polymers which are covalently grafted, chemisorbed, or physically adsorbed to the surface of the water-insoluble polymer particles, and which

comprise pendant vinylsulfonyl or latent vinylsulfonyl groups and are represented by Formula I, and further comprising a bioaffinity tag bound to the porous layer in a spatially addressable manner.

Ogawa relates to an element for electrophoresis, especially to an element for electrophoresis suitably employable for determination of base sequence of DNA, RNA, their fragment, and their derivatives, by disclosing an element for electrophoresis comprising the following three-layer structure laminated in the order:(I) a support layer;(II) an adhesive layer comprising a polymer having at least one specifically selected repeating unit; and (III) a medium layer for electrophoresis comprising an aqueous polyacrylamide gel formed by crosslinking polymerization of an acrylamide compound and a crosslinking agent in the presence of water, and a compound containing at least one carbamoyl group (modifier).

The Applicants believe that Ogawa is non-analogous art. MPEP 2145 indicates that a prior art reference is analogous if the reference is in the field of applicant's endeavor or, if not, the reference is reasonably pertinent to the particular problem with which the inventor was concerned. In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). Ogawa fails to relate to microarrays, especially microarrays having a porous layer composed of a binder and polymer beads. Neither does Ogawa deal with the problem of combining an insoluble bead in a hydrophilic binder to produce a porous layer. Patent and Trademark Office Classification is some evidence of analogy, but similarities and differences in structure and function carry more weight. MPEP 2141.01(a). The reference to Ogawa cited by the Examiner is contained in a different classification. Ogawa is contained in US Class 428/474.7 (Stock Material or Miscellaneous Articles / Next to second layer of polyamide), while the present invention is contained in US Class 435/006 (Chemistry: molecular biology and microbiology / Involving nucleic acid). Critical differences exist in structure between the present invention and the prior art, which is evidence of non-analogousness. Ogawa discloses a three-layer laminated structure of, in order: (I) a support layer; (II) an adhesive layer comprising a polymer having at least one specifically selected repeating unit; and (III) a medium layer for electrophoresis comprising an aqueous polyacrylamide gel formed by crosslinking polymerization of an acrylamide compound and a crosslinking agent in the

presence of water, and a compound containing at least one carbamoyl group (modifier). In the present invention, the group "H" is part of a water soluble polymer grafted to the surface of a water insoluble polymer bead and is contained in the porous layer, not in an adhesive layer connecting the membrane layer to a support. Placement of the "H" group of the present invention in a separate layer and not grafted to the surface of the bead would remove the surface modification that allows the water insoluble bead to be compatible with aqueous systems. Since the cited reference is contained in a different Classification, serves a different purpose and function, and contains distinct structural differences, the Applicants respectfully suggest that the cited reference is non-analogous art, and does not support a rejection based on obviousness.

Assuming for argument, that the cited reference is analogous art, consideration must be given to Applicant's invention and the references as suggested by the Examiner, when taken as a whole. To establish a prima facia case of obviousness requires, first, there must be some suggestion or motivation, either in the references themselves, or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combines) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure. *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

The reference to Sutton fails to teach the modification required by the present invention, that is, the monodispersed particles of the present invention and monodispersed water soluble polymer beads stabilized by vinylsulfonyl-functionalized polymers, which are grafted to the surface of the bead, which are stable and dispersible in aqueous systems. Pierce discloses a plurality of heat-stable, organo-polymeric particles non-swellable in and impermeable to the liquid for use in "dry chemistry" applications, not water insoluble polymer particles that are stabilized by water soluble vinylsulfonyl-functionalized polymers. Pierce also fails to teach a porous layer containing a hydrophilic polymer in combination with a polymer bead, or a hydrophilic polymer in combination with a water-insoluble polymer bead bearing stabilizing, water soluble vinylsulfonyl-functionalized

polymers grafted to the surface of the bead. Glazer teaches a porous layer of, typically, silica particles, but fails to disclose a porous layer containing a hydrophilic polymer in combination with a polymer bead, or a hydrophilic polymer in combination with a water-insoluble polymer bead bearing stabilizing, water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead. Yao discloses appropriately sized particles, but fails to mention the use of hydrophilic binders for use with insoluble beads in the porous layer, teaching instead hydrophobic binders at [0058]. Yao also fails to teach water insoluble particles which are stabilized in water-based systems by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead and fails to teach the presence of bioaffinity tags in the porous layer, placing the tags instead exterior to the layer. See, for example Fig. 1. Obana teaches a polymer particle with a particular size variation, but fails to teach a porous layer of hydrophilic binder and water insoluble beads, water insoluble beads which are stabilized in water-based systems by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead, and fails to mention microarrays. Ogawa discloses a three layer structure containing "H", a vinylsulfone or vinylsulfone precursor unit monomer, which fails to teach a porous layer of hydrophilic binder and water insoluble polymer beads and which positions "H" in a separate layer from the polymeric membrane. Therefore, the references, alone and in combination, fail to teach, suggest or provide a disclosure to modify the references to produce water insoluble polymer beads stabilized by water soluble vinylsulfonyl-functionalized polymers, which are grafted to the surface of the bead.

In fact, the references to Sutton, Pierce and Glazer are not combinable. MPEP 2143.01 Section V states "If proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984)." MPEP 2143.01 Section VI indicates "If the proposed modification or combination of the prior art would change the principle of operation of the prior art invention being modified, then the teachings of the references are not sufficient to render the claims prima facie obvious. In re Ratti, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (The court reversed the rejection holding the "suggested combination of

references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.)." Glazer and Pierce fail to disclose the use of a binder in the porous layer with the particles. Sutton utilizes a binder matrix with the polymer bead. Sutton indicates, at col. 7, lines 28-32, that coating without polymers results in an inoperative element. Sutton specifically mentions that coatings as disclosed in Pierce were inoperative. Accordingly, a combination of glazer and Pierce with Sutton would render the element inoperable or at least so change the principals of operation as to require substantial reconstruction and redesign.

The references also fail to provide any likelihood of success, as there is no teaching to suggest the preparation of particles useful in aqueous systems. None of the references provide a likelihood that the modification of a water insoluble bead with water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead will produce polymer bead, which is stable in aqueous systems and combinable with hydrophilic binders. Pierce teaches the use of the particles in " dry chemistry" systems (col. 1, lines 8-15). Sutton specifically indicates the particles are water-insoluble (Abstract). Glazer, as noted by the Examiner, fails to teach stabilizer polymers attached to the surface of the bead. Yao and Obana fail to mention combining a hydrophilic binder with a water insoluble polymer particle in a porous layer. Ogawa discloses a three layer structure containing "H", a vinylsulfone or vinylsulfone precursor unit monomer, which fails to teach a porous layer of hydrophilic binder and water insoluble polymer beads and which positions "H" in a separate layer from the polymeric membrane, wherein the adhesive layer containing "H" adheres the membrane layer to the support. The references, alone and in combination, fail to provide any likelihood of success in producing a particle, made compatible with hydrophilic binders by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead for use in a porous layer. The Examiner notes benefits such as "*low sensitivity, active groups such as vinylsulfonyl group can be directly attached to polymer particles for covalent attachment of receptor to the particles*," and "*Pierce et al. physically absorbed to the surface of the polymer particles for immobilization of interactive compositions such as antibodies via*

active linking or binding site such as primary and secondary amine groups." These benefits differ from the present invention, in which the purpose of the graft, functionalized polymer is to impart water compatibility to a water insoluble particle, making the particle not only useful in hydrophilic systems, but also resulting in simpler, milder manufacturing conditions. See the present specification, pg. 9, lines 25-30 ("*G is a polymerized α,β-ethylenically unsaturated addition polymerizeable monomer which imparts desirable solubility properties to the polymer or which allows the polymer particles of this invention to be readily dispersed in a carrier solvent (water in most cases)*"); pg. 9, lines 7-12 ("*In an especially preferred embodiment, the polymer particles contain stabilizer polymer comprising pendant vinylsulfonyl or latent vinylsulfonyl groups. Stabilizer polymers having activated vinylsulfonyl groups possess additional advantages in that proteins may be attached to the polymers under milder conditions and utilize less process control during manufacture. This renders manufacture more efficient and less costly.*"); pg. 8, lines 14-19 ("*In a preferred embodiment, the polymer particles are rich in specific functionalities, which impart dispersibility in a desired carrier solvent, compatibility with the microarray's matrix*")

The references also fail to include all of the present claim limitations, since the references fail to disclose porous layer of hydrophilic binder and water insoluble beads, water insoluble beads that are stabilized in water-based systems by water soluble vinylsulfonyl-functionalized polymers grafted to the surface of the bead.

The combination of the references would produce a water-insoluble particle, which would be incompatible in a hydrophilic binder. The present particle, as a result of the grafted vinylsulfonyl-functionalized polymers, which are soluble in water, water-miscible solvents, or a mixture thereof, are stabilized in hydrophilic combination. In addition, the present invention would have increased activity, as indicated in the present specification on pg. 3, lines 3-17, as the present invention combines a scaffold concept with a porous layer. Although, as noted by the Examiner, a porous substrate increases surface area, a porous layer with particles bearing a three-dimensional region of polymer would further increase the surface area available for binding, beyond that available with a porous layer alone.

In summary, the references fail to disclose, teach or suggest the present invention wherein a vinylsulfonyl-functionalized polymer, which is soluble in water, is grafted to the surface of the monodisperse, water insoluble, polymer bead, fail to provide any likelihood of success for the use of monodispersed beads which are stabilized by a vinylsulfonyl-functionalized polymer, which is soluble in water, water-miscible solvents, or a mixture thereof, is grafted to the surface of the monodispersed, water insoluble, polymer bead, resulting in the stability and dispersibility of these grafted polymer particle in aqueous systems, and fails to include the limitation that the polymer beads include a vinylsulfonyl-functionalized polymer, which is soluble in water, water-miscible solvents, or a mixture thereof, grafted to the surface of the monodisperse, water insoluble, polymer bead. The Applicants therefore request that the Examiner reconsider and withdraw the rejection.

Rejection Under 35 U.S.C. §103(a):

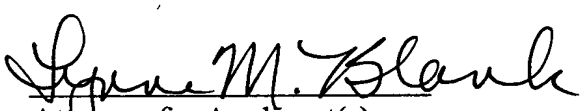
The Examiner has rejected Claim 31 under 35 U.S.C. 103(a) as being unpatentable over Glazer et al. (WO 00/61282, Oct. 19, 2000) in view of Sutton et al. (U.S. Patent No. 5,714,340, Feb. 3, 1998), Yao et al. (U.S. PG Pub. No. US 2003/0100086 Al, filed May 30, 2001), and Obana (U.S. Patent No. 4,605,686, Aug. 12, 1986) and in light of Pierce et al. (U.S. Patent No. 4,258,001, Mar. 24, 1981) as applied to claims 1 and 27 above, and further in view of Li et al. (U.S. Patent No. 5,288,763, Feb. 22, 1994), as Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. teaches a microarray comprising a stabilizer polymer as discussed above, and, although Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. fails to teach polymeric particle comprising at least one ethylenically unsaturated polymerizable monomer comprising ethylene glycol dimethacrylate, Li et al. teaches polymer particles comprising cross-linkers, which include ethylene glycol dimethacrylate, the cross-linking is responsible for making the polymer particles substantially insoluble in any solvents, including strong acidic or alkaline solution, the polymer particles of Li are useful in variety of analytical, diagnostic techniques as well as solid state peptide and DNA synthesis, making it obvious to one of ordinary skill in the art at the time of the invention to include in the polymer particles of Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. with cross-linking polymers such as ethylene glycol

dimethacrylate during the process of making the polymer particles as taught by Li et al. in order to provide polymeric particles, which are substantially insoluble in any solvents, including strong acidic or alkaline solution as a result of cross-linking, as the advantage of having polymeric particles, which are substantially insoluble in any solvents, including strong acidic or alkaline solution as a result of cross-linking provides the motivation to combine the teachings of Glazer et al. in view of Sutton et al., Yao et al. and Obana et al. and in light of Pierce et al. and Li et al. with reasonable expectation of success as the polymeric particles with cross-linking polymers can be used in a variety of analytical and diagnostic assays.

Claim 31 benefits from dependence on claim 1, which as discussed above, Applicants believe is non-obvious with respect to the references.

It is believed that the foregoing is a complete response to the Office Action and that the claims are in condition for allowance. Favorable reconsideration and early passage to issue is therefore earnestly solicited.

Respectfully submitted,



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